

ANCA- positive IgA nephropathy presented as alveolar hemorrhage in a COVID-19 patient

ANCA positive IgA nephropathy in COVID-19

Hakan Apaydin¹, Serdar Can Güven¹, İsmail Doğan¹, Aysel Çolak², Şükran Erten¹

¹Department of Rheumatology, Ankara City Hospital

²Department of Pathology, Ankara City Hospital, Ankara, Turkey

Abstract

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The SARS-CoV-2 virus primarily targets the respiratory system, but extrapulmonary involvements can be frequently seen. We presented a COVID-19 case with anti-neutrophil cytoplasmic antibody-positive IgA nephropathy, alveolar hemorrhage, and rapidly progressive kidney disease. The patient received pulse corticosteroids, plasma exchange, and intravenous immunoglobulin as treatment. Azathioprine was added as an immunosuppressive therapy. To the best of our knowledge, this is the first reported case of IgA nephropathy coexisting with COVID-19 infection.

Keywords

Alveolar hemorrhage; ANCA; COVID-19; IgA nephropathy; Intravenous immunoglobulin; Plasmapheresis

DOI: 10.4328/ACAM.20424 Received: 2020-12-03 Accepted: 2021-01-03 Published Online: 2021-01-10 Printed: 2021-06-15 Ann Clin Anal Med 2021;12(Suppl 2): S236-240

Corresponding Author: Hakan Apaydin, Ministry Of Health Ankara City Hospital, Department of Rheumatology, Ankara, Turkey.

E-mail: drhakanapaydin@gmail.com P: +90 5423498009

Corresponding Author ORCID ID: <https://orcid.org/0000-0001-7219-1457>

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people and caused thousands of deaths. SARS-CoV-2 is known to cause significant pulmonary diseases, including pneumonia and acute respiratory distress syndrome (ARDS), and may also present with diffuse alveolar hemorrhage (DAH) [1]. DAH can complicate many clinical situations and can be life-threatening, requiring immediate treatment.

Various extrapulmonary manifestations of COVID-19 have been reported. Acute kidney injury (AKI) is commonly reported in the COVID-19 course [2]. IgA nephropathy (IgAN) is the most prevalent form of primary glomerulonephritis and a significant cause of chronic kidney disease and end-stage renal failure. Infectious diseases are a known cause of IgAN, however, the relation with COVID-19 has not yet been clarified.

Herein, we report a COVID-19 case presented with rapidly progressive kidney failure and alveolar hemorrhage during disease course with positive antineutrophil cytoplasmic antibodies (ANCA) and a kidney biopsy specimen highly suggestive of IgAN.

Case Report

An 18-year-old male patient without any remarkable medical history was admitted to the emergency department on September 7 with fever, cough, and malaise. On admission, the patient was conscious and cooperative, with a blood pressure of 124/54 mm Hg, a heart rate of 98 beats per minute, a body temperature of 37°C, and a respiratory rate of 20 per minute. Oxygen saturation on room air was 94%. Laboratory results were as follows: hemoglobin 14.1 g/dL (12.2-18.1), platelet and white blood cell (WBC) count was normal, lymphocytes count 660 (1100- 4500), creatinine 0.96 mg/dL (0.67-1.17), C-reactive protein (CRP) 86 mg / dL (0-5), liver function tests, cardiac enzymes, ferritin, procalcitonin, coagulation parameters were normal. Serum immunoglobulin levels were within normal ranges.

The patient was diagnosed with COVID-19 with a positive nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) test. The patient was then hospitalized, and was prescribed favipiravir, hydroxychloroquine, and low-molecular-weight heparin (LMWH).

The next day, the patient developed hemoptysis of 30-40 cc at a time with a total bleeding of 2-3 cups. O₂ saturation was 95% with 2 L/min nasal oxygen. Repeated laboratory evaluation revealed decreased hemoglobin (8.1 gr/dL) and elevated serum creatinine (1.20 mg/dL). In the urinalysis, 140 erythrocytes, 5 leukocytes were detected, the spot urine protein/creatinine ratio revealed a protein excretion of 987 mg/day. In the urine sediment, abundant isomorphic erythrocyte, granular and leukocyte casts were observed. Computed tomography (CT) of the chest revealed fused consolidation and infiltrations in the form of ground-glass opacity, which were common in both lungs, especially in the left lung. This was interpreted primarily in favor of diffuse hemorrhage (Figure 1). The patient was then admitted to the intensive care unit and LMWH treatment stopped. Serum creatinine level further increased to 1.86 mg/dL and O₂ saturation dropped to 82%, requiring high-flow oxygen therapy. Further laboratory tests were negative for anti-nucleated antibodies, anti-dsDNA, anti-extractable nuclear antigens panel, and anti-glomerular basal membrane antibody, but positive for proteinase 3 (PR3) – ANCA in indirect immunofluorescence assay (IFA) (1/320) and positive for PR3-ANCA in enzyme-linked immunosorbent assay (ELISA) (> 200 RU/mL). Serum complement 3 level was low and complement 4 level was normal. The patient was then consulted by the rheumatology department.

At presentation, the patient had rapidly progressive kidney disease and active urinary sediment, chest CT findings primarily suggested alveolar hemorrhage and a positive PR3-ANCA ELISA test. The patient was considered as ANCA associated pulmonary-renal syndrome possibly triggered by COVID-19 infection. Pulse methylprednisolone 1000 mg/day for three days was started, followed by 60 mg/d, and fresh frozen plasma exchange every

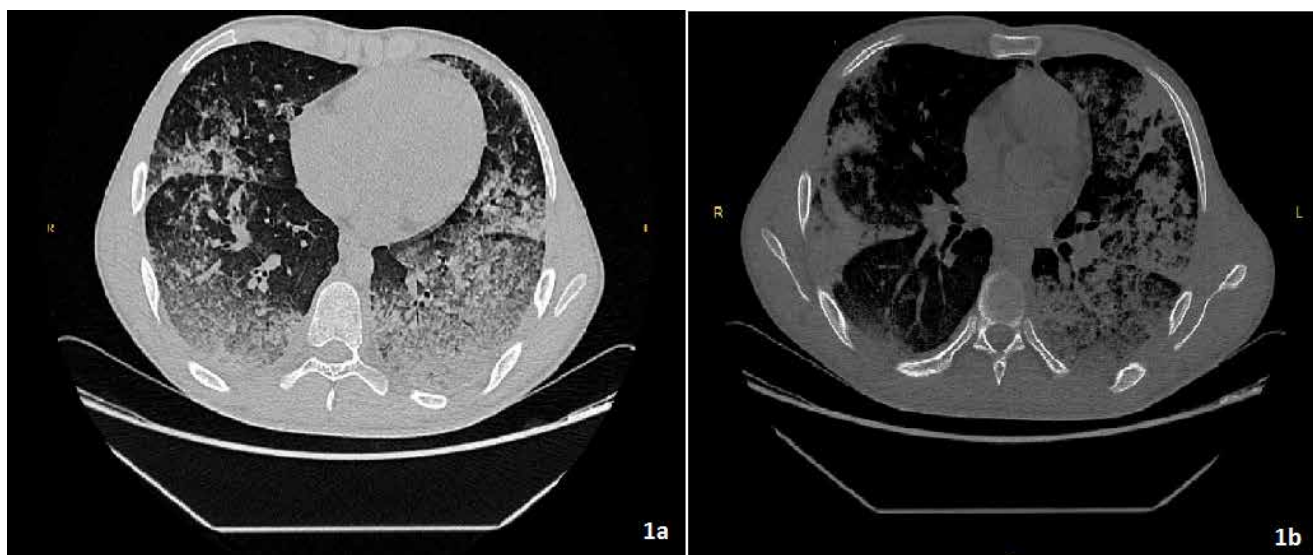


Figure 1. Chest CT. A: Lung window: Fused consolidation and infiltrations in the form of ground-glass opacity were common in both lungs, especially in the left lung. Septal thickening and air bronchograms accompanied these infiltrations. These findings are suggestive of diffuse alveolar hemorrhage. B: Mediastinal window



Figure 2. Chest X-ray (PA view).

A: Diffuse bilateral middle and lower zone heterogeneous opacity (September 8)

B: There is a decrease in infiltrates and opacities (September 21)

C: Complete recovery (October 4)

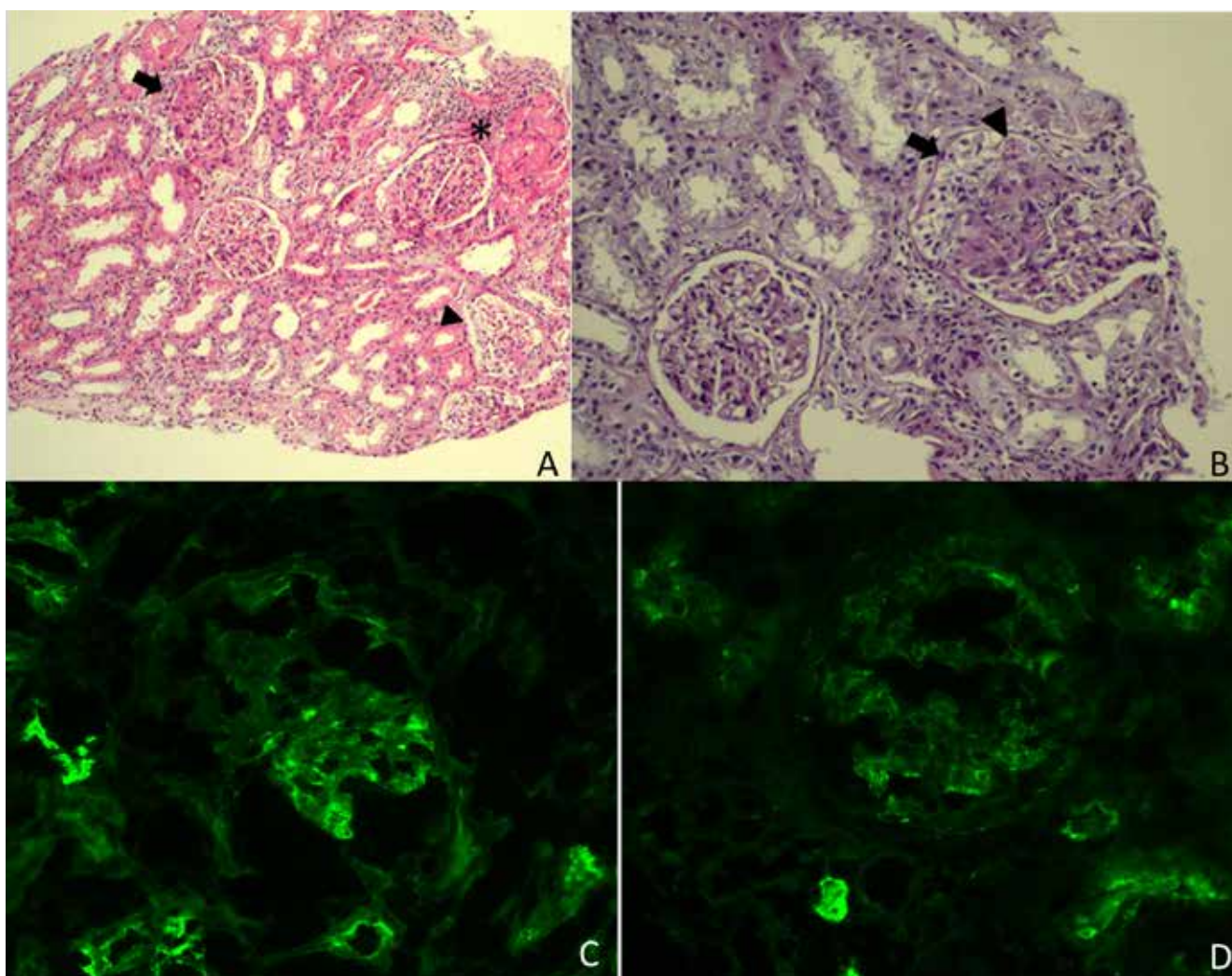


Figure 3. A: Cellular crescent (arrow), early crescent formation (arrowhead) and segmental sclerosis - tip lesion (asterisk) characterized by the adhesion of the capillary tangle to the Bowman capsule (Hematoxylin and Eosin x100)

B: Cellular crescent (arrow) and fibrinoid necrosis (arrowhead) (PAS x200)

C: IgA staining in immunofluorescence study

D: C3c staining in immunofluorescence study

day for seven courses by initiating on September 9. Intravenous immunoglobulin (IVIG) therapy at a dose of 0.4 g/kg/day was given to the patient for five days after the plasma exchange regimen completed. The favipiravir and hydroxychloroquine regimens were simultaneously completed for up to five days. Pulmonary findings rapidly regressed, hemoptysis did not recur, the patient was no more O₂-dependent, and CRP levels lowered to the normal range. A significant regression was observed on chest radiography (Figure 2). However, the serum creatinine level continued to progress, reaching over 3 mg/dL.

On the 14th, 15th and 16th of September, the patient's COVID-19 PCR tests were negative. The patient was transferred from the intensive care unit to the rheumatology clinic. A kidney biopsy was scheduled due to the persistent elevation in the serum creatinine level. On September 29, a tru-cut biopsy was performed from the lower pole of the right kidney, revealing fibrocellular crescent in one glomerule, an early stage of cellular crescent morphology in one glomerule, and segmental sclerosis in one glomerule. Fibrinoid necrosis accompanied crescentic glomeruli. In some other glomeruli, mild mesangial cellular proliferation and an increase in the thickness of the basement membranes in one glomerule were noted. In the immunofluorescence examination, focal, mesangial coarse granular staining with IgA, IgM and C3 complement was observed. The renal biopsy was compatible with IgA nephropathy (Figure 3).

During the follow-up of the patient, the serum creatinine level increased to 1.15 mg/dL. Methylprednisolone 60 mg/d was planned to be continued for one month, and to be tapered gradually thereafter. On October 15, azathioprine 150 mg / day was added to the treatment as an immunosuppressive and steroid-sparing agent. The patient was discharged on October 19.

Discussion

Herein, we described an 18-year-old male COVID-19 patient presented with diffuse alveolar hemorrhage and acute renal failure diagnosed as ANCA positive IgAN.

There is growing evidence of extrapulmonary manifestations of COVID-19. In the United States, the incidence of AKI in patients hospitalized with COVID-19 has been reported to be around 37% [2]. IgAN was the most common primary glomerulonephritis worldwide. The clinical manifestations of IgA nephropathy can vary widely. However, asymptomatic hematuria and progressive loss of kidney function are common.

ANCAs are serologic markers of ANCA-associated vasculitis (AAV) and play an important role in the pathogenesis of various autoimmune diseases. There are a number of reports about patients with IgAN and seropositive ANCA. Bantis et al. defined a case series of 8 patients with a total of 393 patients with IgA nephropathy diagnosed by kidney biopsy (2.04% prevalence) [3]. Among them, five had anti-MPO, and three had anti-proteinase 3 (PR3) antibodies. All patients presented with the clinical syndrome of rapidly progressive glomerulonephritis and reached a peak serum creatinine level of 4.2±2.2 mg/dL in the first 3 months versus 2.5±1.9 mg/dL in ANCA-negative patients. Furthermore, ANCA-positive patients had a higher percentage of crescent glomeruli (54.3% vs 34.5%)

than ANCA-negative patients. ANCA-positive patients treated with intensive immunosuppressive medications (consisting of cyclophosphamide and corticosteroids) demonstrated substantial improvement in renal function. Contrarily, only a minority of the ANCA-negative group received aggressive therapy (5/26); the other patients received steroids alone, mycophenolate mofetil or angiotensin-converting enzyme inhibition. All of these patients demonstrated further progression of kidney failure during the 6-month follow-up period. Yang et al. demonstrated that ANCA-positive IgAN patients had more severe clinical and histological characteristics than ANCA-negative IgAN patients, and their renal prognosis was relatively better with aggressive immunosuppressive therapy in the short term [4]. These studies have shown that ANCA-positive IgAN patients may respond very well to immunosuppressive therapy, and it is similar to the regimens used in patients with classical ANCA-positive vasculitis with renal involvement.

IVIG is a biological product including polyclonal immunoglobulin G. IVIG has been shown to inhibit ANCA-induced neutrophil activation and cytokine release in vitro, and anti-idiotypic antibodies against ANCAs have been explored in IVIG preparations [5]. In addition, IVIG has been used successfully in AAV with relapsing disease and refractory disease [6]. In Wuhan, in a small case series of 3 patients who had deteriorated due to COVID-19, they showed clinical and radiographic improvement with the onset of IVIG [7]. Therefore, we used IVIG due to its successful results in COVID-19 disease and AAV.

Plasma exchange has been successfully used in anti-GBM disease, AAV, SLE, and other autoimmune disorders [8]. In the study conducted by Klemmer et al., in 20 patients who received a combination of intravenous immunosuppressive therapy and plasma exchange in patients with small-vessel vasculitis, DAH showed 100% recovery and some improvement in renal function [8].

In the present case, our patient improved after pulse methylprednisolone, seven plasma exchange sessions and intravenous immunoglobulin. The patient's renal function improved and the DAH recovered completely. Due to the simultaneous COVID-19 infection, the use and timing of immunosuppressive therapy should have been chosen carefully in this life-threatening condition.

Infections are known to trigger AAV and IgAN. This case highlights that SARS-CoV-2 could be the trigger for IgAN and AAV, and this should be kept in mind in such cases. Although ANCA-positive patients have a more severe course, their response to aggressive immunosuppressive therapy is excellent. Therefore, ANCA antibodies should be determined in all patients with IgA nephropathy, and in cases with COVID-19, treatments such as IVIG, pulse steroids and plasma exchange can be applied, depending on the disease severity.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical

standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Löffler C, Mahrhold J, Fogarassy P, Beyer M, Hellmich B. Two Immunocompromised Patients With Diffuse Alveolar Hemorrhage as a Complication of Severe Coronavirus Disease 2019. *Chest*. 2020;158(5):e215-19. DOI:10.1016/j.chest.2020.06.051
2. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int*. 2020;98(1):209-18. DOI:10.1016/j.kint.2020.05.006
3. Bantis C, Stangou M, Schlaugat C, Alexopoulos E, Pantzaki A, Memmos D, et al. Is presence of ANCA in crescentic IgA nephropathy a coincidence or novel clinical entity? A case series. *Am J Kidney Dis*. 2010;55(2):259-68. DOI:10.1053/j.ajkd.2009.09.031
4. Yang YZ, Shi SF, Chen YQ, Chen M, Yang YH, Xie X-F, et al. Clinical features of IgA nephropathy with serum ANCA positivity: a retrospective case-control study. *Clin Kidney J*. 2015;8(5):482-8. DOI:10.1093/ckj/sfv078
5. Rossi F, Jayne DRW, Lockwood CM, Kazatchkine MD. Anti-idiotypes against anti-neutrophil cytoplasmic antigen autoantibodies in normal human polyspecific IgG for therapeutic use and in the remission sera of patients with systemic vasculitis. *Clin Exp Immunol*. 1991;83(2):298-303. DOI:10.1111/j.1365-2249.1991.tb05631.x
6. Jayne DRW, Chapel H, Adu D, Misbah S, O'donoghue D, Scott D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *QJM*. 2000;93(7):433-9. DOI:10.1093/qjmed/93.7.433
7. Cao W, Liu X, Bai T, Fan H, Hong K, Song H, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *Open Forum Infect Dis*. 2020;7(3):102. DOI:10.1093/ofid/ofaa102
8. Klemmer PJ, Chalermkulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. *Am J Kidney Dis*. 2003;42(6):1149-53. DOI:10.1053/j.ajkd.2003.08.015

How to cite this article:

Hakan Apaydın, Serdar Can Güven, İsmail Doğan, Aysel Çolak, Şükran Erten. ANCA- positive IgA nephropathy presented as alveolar hemorrhage in a COVID-19 patient. *Ann Clin Anal Med* 2021;12(Suppl 2): S236-240